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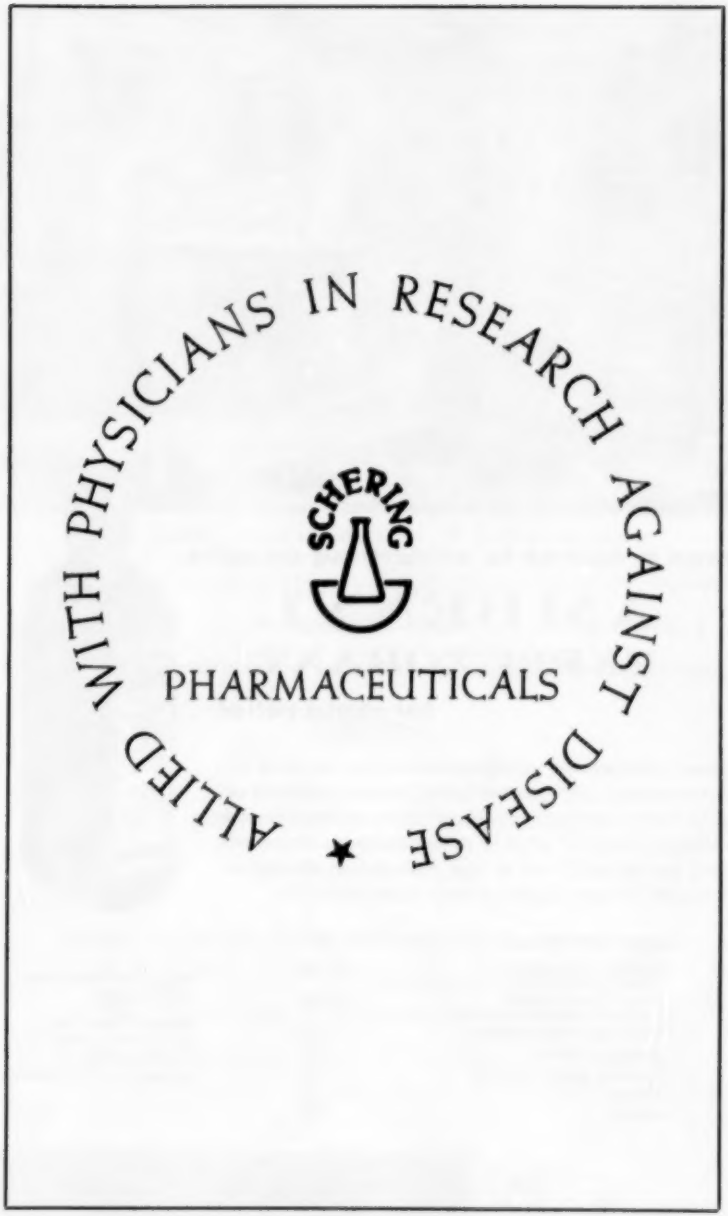
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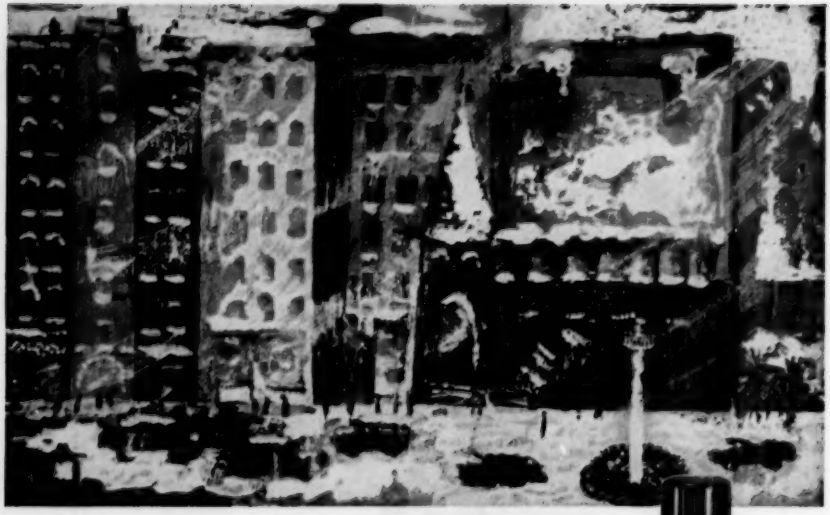

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E D I T O R I A L

LET'S BE RATIONAL

IN the efforts of some well-intentioned persons to curb the pernicious and unethical practice of substitution, certain positions have been taken and statements made which must not go unchallenged.

We are firmly opposed to substitution in all forms, whether it be the dispensing of counterfeit items or brand substitution unknown to and unauthorized by the prescribing physician. So, too, are we opposed to the ARB plan which we attacked editorially on these pages when it was a much discussed issue and before it was properly laid at rest.

There are, however, certain prerogatives belonging to every pharmacist which are irrevocably his and must remain so. These, when grouped in the same category as substitution, do much to weaken the case against substitution and may even alienate many honest and conscientious pharmacists from the forces now opposing it. It is to certain of these prerogatives that we wish to draw attention.

Any and every pharmacist has the inalienable right, when some brand of a drug is prescribed, to ask the physician for his authorization to dispense a brand other than prescribed. It is not always feasible to stock every brand of every drug; in fact, it is impossible. Now, it is, of course, assumed that the brand suggested in place of that prescribed is a good one and that the approval of the physician is obtained in each specific instance and not as a blanket authorization. To argue that this is wrong has even less merit than the pharmacist's frequent argument that a manufacturer hasn't the right to duplicate something already on the market. To deny either would be contrary to our free economic system.

Another inviolate right of the pharmacist is to suggest to the physician that an *identical* drug sold under a variety of trade names be prescribed under its generic name or official title. This permits the pharmacist to dispense the brand in stock without the necessity of obtaining the physician's approval. As a case in point, we might take the drug tetracycline. Not only is this a costly drug but there are presently 5 brands identical in composition—some even being sup-

plied to a given manufacturer by a competing company under license. Such a practice should not be confused with the ARB plan which suggested the use of *brand names followed by ARB*. This, we are against.

If we are not in error, we believe it to be standard practice to teach medical students to use official titles on their prescriptions and such a practice is in accordance with the Code of Ethics of the American Medical Association. There is, furthermore, nothing in the Code of Ethics of the American Pharmaceutical Association against this.

While we can understand the unhappiness which this causes companies who strive hard to have their brand name used at all times, it is a little ridiculous to hear them cry out in anguish at the suggestion that this is not ethically or morally wrong. Their attitude on this then becomes as lacking in judgment and objectivity as that of retailers who argue that restrictions should be placed on the number of brands allowed on the market.

This is still a relatively free country and private enterprise, still an accepted economic policy. No group should expect the privileges and opportunities which the system provides without facing a few of its hazards. To impugn the ethics or morals of those who are acting within their professional or commercial rights is in bad taste. There is much to be done in cleaning up the nasty substitution situation without tilting at windmills.

L. F. Tice

MODERN MEDICINALS IN REVIEW

By Robert E. Abrams * and Linwood F. Tice **

CONTINUING progress in pharmaceutical research and development characterized the year 1954. Although it appears that the year 1954 was not as dramatic as other recent years, there were enough new excellent therapeutic products developed to indicate great progress and that the future in drug therapy is indeed bright. As usual, there were a large number of combinations made available, but in this review we have attempted only to cover new major therapeutic advances. It is physically impossible to list all the products released, but the following may give some indication of the direction of pharmaceutical research.

Adrenergic Blocking Agent

A new adrenolytic, azapetine hydrochloride (*Ilidar* Hoffmann La-Roche Inc.), has been made available for the treatment of vasospasm. Claimed to have a fourfold effect, it acts by causing dilation of the peripheral blood vessels by sympatholytic and adrenolytic action, epinephrine reversal, and by direct vasodilation.

Available in 25 mg. coated tablets, *Ilidar Phosphate* is particularly useful in symptomatic relief of circulatory conditions characterized by aching, coldness, tingling and numbness of the extremities. The usual dose is one to four tablets daily as required by the individual patient.

Amebicides

Still a persistent problem, the treatment of amebiasis has responded favorably to many therapeutic agents developed over the past years including the isoquinolines (Diodoquin, Vioform), bismuth glycolylarsanilate (Milibis) and the broad spectrum antibiotics. The latest to be released is *Mantomide* (Winthrop-Stearns) which is claimed to be more highly active in considerably smaller doses against

* Assistant Professor of Pharmacy, Philadelphia College of Pharmacy & Science, Executive Secretary, American College of Apothecaries.

** Director, Department of Pharmacy and Assistant Dean, Philadelphia College of Pharmacy & Science.

Endamoeba histolytica than other drugs. Chemically it is N-(2,4-dichlorobenzyl)-N-(2 hydroxyethyl) dichloracetamide.

It is supplied in tablets containing 250 mg. The dose is adjusted to the patient's age. For patients less than five years, 250 mg. three times daily for eight days represents a usual schedule. Those patients between 5 and 10 years of age receive 500 mg. three times daily for ten days; and for those over 10 years, 750 mg. to 1.0 Gm. three times daily for 10 and 8 days respectively. The drug appears to be relatively non-toxic and well tolerated.

Another highly effective drug is now under clinical evaluation. Known as *Camoform* (Parke, Davis & Co.) it was originally synthesized as an antimalarial agent. Initial clinical and laboratory trials indicate the possibility that the drug may be effective against both intestinal and extraintestinal amebiasis.

Analgesic

An injectable non-narcotic analgesic compound with rapid and prolonged activity has been introduced under the name of *Pyridone* (Geo. A. Breon & Co.) Chemically, it is sodium 1-phenyl-2,3-dimethyl-4-methylaminopyrazolon-N-methanesulfonate. The drug is indicated in cases of acute pain since it is claimed to possess a rapid and prolonged analgesic action. It is particularly suggested for injection in rheumatic fever when patients cannot tolerate salicylates.

Side effects seem to be minimal and the drug does not cause any respiratory depression. It is available in 200 mg. ampuls and is injected either subcutaneously or intramuscularly in doses of 1-2 cc. repeated if necessary in two to three hours.

Anthelmintic

A relatively old chemical compound, piperazine hexahydrate has been shown to be a most effective treatment for *oxyuriasis* (pinworm). Originally introduced as the piperazine citrate by Burroughs and Wellcome under the name of *Antepar Syrup*, it is also available from numerous other sources. Containing the equivalent of 100 mg. of the hexahydrate per cc., *Antepar* is usually administered for 7 days; the next seven days are allowed to elapse without medication; then it is given again for the following seven days. The dose ranges from 2.5 cc. daily for a very small child to 10 cc. daily for an adult. It is

usually administered twice daily and may be given with orange juice or other liquids in the diet.

The drug appears to be well tolerated and clinical investigators have found up to 85% cure rate in studies undertaken. Recent studies have also shown it to have promise as an ascaricide.

Antibiotics

Tetracycline

It now seems quite likely that the parent substance tetracycline is superior for most uses to its close relatives, chlortetracycline and oxytetracycline. Its primary advantages seem to lie in its better absorption and fewer side effects, as well as its greater stability. Presently it is being supplied as *Achromycin* (Lederle), *Tetracyn* (Pfizer), *Polycycline* (Bristol), *Steclin* (Squibb) and *Panmycin* (Upjohn). A wide range of dosage forms are available including capsules, tablets, oral suspension, pediatric drops, soluble tablets, "readymixed" suspension, an injectable form, otic solution, ointment, and ophthalmic ointment.

Since the spectrum of tetracycline is similar to chlortetracycline and oxytetracycline, cross resistance among the three compounds is to be expected and has been demonstrated.

Mycostatin

The overgrowth of monilia in the gastrointestinal tract has frequently been reported during the use of the broad spectrum antibiotics. This is believed to occur due to the destruction of the normal inhabitants of the intestine, the coliform organisms, which are susceptible to the broad spectrum antibiotics. The organism most frequently found associated with this condition is *Candida albicans*. The symptom manifestations range from stomatitis to intense diarrhea often followed by perianal abscess or fissuring. In addition, systemic monilia infection may occur with a very poor prognosis.

A new antibiotic obtained from cultures of *Streptomyces noursei* has been shown to be very active against intestinal moniliasis. Available as *Mycostatin* (Squibb) the drug is recommended as an adjunct to broad spectrum antibiotic therapy to prevent the overgrowth of monilia. The drug is supplied in 500,000 unit tablets and is administered one or two, 3 times daily, preferably given with the broad spectrum antibiotic as a prophylactic measure.

Erythromycin

This antibiotic was employed very frequently in 1954; particularly, in penicillin-resistant infections and for certain topical infections. Various new dosage forms were made available including a 200 mg. tablet and a parenteral form. In addition, oral products combined with sulfonamides are available and topical products particularly combined with neomycin have been released.

Antibiotic Combinations

The combination of several antibiotics to strengthen their antibacterial action and extend their effect has grown in popularity. This is particularly true in products intended for topical use where mixed infections are frequently observed. Some examples of such products are: *Wybiotic Troches* (Wyeth) which contain zinc bacitracin, neomycin and polymyxin B sulfate; *Tetrazets* (Sharp & Dohme) containing bacitracin, tyrothricin and neomycin sulfate; *Neosporin Ointment*, which contains polymyxin B sulfate, bacitracin and neomycin; and the various erythromycin combinations previously mentioned.

Penicillin

A long acting form of penicillin similar in nature to Benzathine has been made available under the name of *Compocillin* (Abbott). Originally known as Hydrabamine penicillin G, the product is a rosin amine salt of low solubility and is effective against penicillin susceptible organisms. It is presently available in suspension form.

Benethamine penicillin originally introduced in England, probably will also be available soon. It is a repository penicillin intermediate between procaine penicillin and benzathine penicillin in its duration of action.

Antibiotics Under Trial

Many new antibiotics were discussed at the Antibiotic Symposium held in 1954. Included in the group were *Actinomycin-C* (Schenley) which has shown some antitumor activity in man and animals.

Clesticetin (Upjohn) which is active against micrococci, streptococci, pneumococci and clostridia.

Fungichromin and Fungichromatin (Sharp & Dohme) are antifungal agents active against a variety of molds including *Candida albicans* and *Aspergillus niger.*

Anisomycin (Pfizer) is effective against such protozoa as *Trichomonas vaginalis, Trichomonas foetus* and *Endamoeba histolytica.*

Puromycin (Lederle) shows activity against *Endamoeba histolytica.*

Etamycin (Bristol) protects mice infected with *diplococcos pneumoniae.*

Spiramycine (Rhone-Poulenc) has shown value in treatment of gram-positive infections.

Griseoviridin and *viridogrisein* (Parke, Davis) the first has been shown to be effective against *H pertussis* in mice; the second active against staphylococcal and streptococcal mastitis in cows, staphylococcal infections in mice and amebiasis in rats and dogs.

Anticoagulant

Under license by the Wisconsin Alumni Research Foundation Endo has made available *Coumadin* in both parenteral and oral form. The injection contains in each 10 cc., 75mg. and the tablets 25 mg. of Warfarin sodium, sodium 3(alpha-phenyl-beta-acetylethyl)4-hydroxy coumarin. Warfarin was originally introduced as a rodenticide and believed too toxic for use in clinical medicine. Recent studies have indicated the product to be a safe and effective anticoagulant giving a more rapid onset of action and a shorter duration of action than dicoumarol.

Anticonvulsants

Two new products have been introduced over the past year for the control of epilepsy. The first of these primidone (*Mysoline*—Ayerst Laboratories) is 5-phenyl-5-ethyl-hexahydropyrimidine differing from phenobarbital in not having a ketone group at position 2 on the pyrimidine ring. The drug is specifically recommended in the control of grand mal and psychomotor seizures. It is supplied in tablets containing 0.25 Gm. The suggested dosage in adults or children over

8 years is 0.25 Gm. daily increasing gradually at weekly intervals until maximum therapeutic effect is achieved. Doses over 2 Gm. daily, however, are not recommended.

The second product in this category is the compound N-methyl-alpha-phenylsuccinimide marketed as *Milontin* by Parke, Davis & Co. This drug is suggested in the treatment of petit mal epilepsy and is supplied in Kapseals containing 0.5 Gm.

Anti-Infectives

On October 1, 1954, gamma globulin was released for distribution through retail outlets and decontrolled by the Federal Office of Defense Mobilization. Suggested for the possible prevention of paralytic polio, measles and infectious hepatitis, the product is presently available through a number of companies. Those supplying the product in 2 cc. and 10 cc. vials include Sharp and Dohme, Lederle, Cutter and Pitman Moore.

Studies seem to indicate that gamma globulin can prevent paralytic polio in certain cases; particularly, where it is used early enough and in proper dosage. However, from all indications its usefulness may be greatly surpassed by the development of the polio vaccine now undergoing clinical trial. Its effectiveness in measles and infectious hepatitis, however, has been known and utilized for some time and it is in this direction that it will probably be used most widely.

Antirabies Serum

While rabies vaccine is standard treatment for a person bitten by a rabid animal, it has been a prophylactic measure accompanied by some difficulties. The large repeated doses of the vaccine are poorly tolerated and may cause a post-vaccinal neuroparalysis. Furthermore, should the patient be bitten around the face or neck, the antibody response may be too slow to offset the rapid invasion of the virus. A new adjunct to rabies vaccine has been released by Lederle Laboratories as *Antirabies Serum*. This is a refined and concentrated serum derived from hyperimmunized horses. It is recommended for use with rabies vaccine in the prophylactic treatment of all individuals who have been exposed to possible rabies infection. It provides an extra margin of safety and may reduce the number of injections of rabies vaccine needed. Antirabies Serum is supplied in 1,000 unit vials.

Antihypertensives

Rauwolfia and its derivatives

Probably one of the most rapid developments this past year has been the extensive use of *Rauwolfia serpentina* and its alkaloids in the treatment of hypertension. Although there is a tendency by many physicians to employ the alkaloidal fractions, some still believe the whole root represents a better therapy in that it does not provide as much tranquilizing effect. A number of products containing the pure alkaloid have been released including *Serpasil* (Ciba), *Reserpoid*, (Upjohn), *Rau-Sed* (Squibb), *Sandril* (Lilly), *Serfin* (Parke, Davis) and *Serpiloid* (Riker).

The hypotensive effect of these products is slow in developing and is not as great as that produced by drugs such as the ganglionic blocking agents. Its mechanism of action, at least in part, is probably through a depressant or tranquilizing effect on the hypothalamus. This tranquilizing effect is also being used in neuropsychiatry where the drug is being employed in psychoneuroses and related conditions, as well as in psychoses and in the tense or anxious patients. It has a tendency to quiet the restless or combative patient and has helped decidedly where psychiatric treatment is employed.

The only known contraindication to the drug is in peptic ulcer since it does increase gastric secretion. It may be employed in these patients provided adequate dosage of an antisecretory agent is concommitantly administered. The drug, however, may produce nasal congestion, drowsiness, diarrhea and occasionally bizarre dreams. These side effects are usually transient or may be controlled by reduced dosage.

Rauwolfia seems to be effective only in the relatively mild cases of hypertension when used alone. However, when combined with the more potent antihypertensive agents, it seems to be more valuable. Thus we have available such combinations as *Serpasil-Apresoline* (Ciba), *Methium with Reserpine* (Warner Chilcott), *Nitranitol R. S.* (Merrell), *Veralba-R* (Pitman Moore), and *Rauwiloid* and *Hexamethonium* (Riker). In addition, recent reports indicate that combinations of chlorpromazine and reserpine show great promise both in hypertension and in neuropsychiatry.

In an effort to ameliorate the nasal stuffiness associated with the use of Rauwolfia preparations, Eli Lilly and Company have made

available *Sandril* with *Pyronil*. The inclusion of Pyronil neither affects the hypotensive action nor modifies any other therapeutic effects of the reserpine.

Riker Laboratories have announced the separation of a new antihypertensive alkaloid, rescinnamine, from the alseroxylon fraction of Rauwolfia. It is the 3, 4, 5-trimethoxycinnamic acid ester of methyl reserpate and has been shown to have a hypotensive, bradycrotic and sedative activity similar to that of reserpine and Rauwiloid. It is also reported to be more hypotensive and less sedative than reserpine.

Ansolysen

A new ganglionic blocking agent, pentolinium tartrate (*Ansolysen*—Wyeth), appears to be superior to hexamethonium; at least by the oral route, in the treatment of moderately severe, severe and malignant hypertension. Chemically, pentolinium is pentamethylene 1,5-bis (1-methyl-pyrrolidinium) bitartrate. Its primary advantage seems to reside in the fact that it offers more uniform and predictable response on oral administration and also in that it provides a longer duration of action.

The use of the ganglionic blocking agents is increasing as the physician learns more about the method of adjusting dosage. In all patients the dose of pentolinium must be individualized and many practitioners are utilizing the drug in combination with reserpine to minimize the necessary dose. The dose of *Ansolysen* must be adjusted with accuracy. A little too much may produce postural hypotension and too little may produce an inadequate fall in blood pressure. Office blood pressures may be misleadingly high and more physicians are becoming dependent on home recordings by the patient's family to establish a more accurate criterion of proper dosage.

The use of the drug is not without some dangers. Constipation, although not as severe as with hexamethonium, still must be prevented. The use of pilocarpine, neostigmine orally, or a laxative in conjunction with the administration of the ganglionic blocking agents is frequently needed. Cycloplegia may occur, although it is usually temporary. Dryness of the mouth may occur and this also may be controlled with pilocarpine.

Ansolysen is supplied in 40 and 100 mg. tablets and in an injection form containing 10 mg. per cc.

Antispasmodics

A number of varied combinations of antispasmodics was made available during the past year and two new compounds were released.

The first of these has been under experimental use for a number of years. Originally known as MK-02, it is now available as *Cogentin* from Sharp and Dohme and has been shown to be effective for the relief of the tremor and rigidity of Parkinsonism. Studies indicate that in certain cases extensive muscular rigidity, muscle spasm and contracture may be overcome with the use of the drug. *Cogentin* may be given alone or in conjunction with other drugs. In fact, the manufacturer suggests that it be given simultaneously with another drug to control a specific condition like rigidity if the patient has been taking the other drug without full relief.

It is available in 2 mg. tablets and is recommended in all types of Parkinson's syndrome. It is administered once daily upon retiring when used in conjunction with other drugs.

The second drug in this classification is somewhat different in effect and is recommended for upper gastrointestinal pain and spasm, for cardiospasm, gastroduodenal spasm, biliary spasm, pylorospasm and gastro neurosis and irritability. Known as *Dactil* (Lakeside Laboratories) it is N-ethyl-3-piperidyldiphenylacetate hydrochloride. It is available in 50 mg. capsules and the suggested dosage is one, four times a day. It is claimed to have certain advantages in that it is rapidly acting, will not interfere with the normal action of the smooth muscle of the gut and is unusually well tolerated.

Antitussives

Merck and Company has announced the availability of *Narcotine* in bulk for use by pharmaceutical manufacturers. Originally obtained in pure form over a century ago, it was thought to have no medicinal value. However, recent studies indicate that it has distinct antitussive properties and is non-habit forming, non-constipating and without effect on blood pressure or respiration. It is suggested to be used in syrups, lozenges, tablets and capsules.

Another antitussive compound was introduced in 1954; namely, *Romilar Hydrobromide* (Hoffmann La Roche). It is made synthetically and is *d*-3-methoxy-N-methylmorphinan hydrobromide. Being non-habit forming it does not come under the Harrison Narcotic Act. It is a potent cough inhibitor, which offers the anti-

tussive action of codeine without its analgesic and narcotic properties. It is claimed that a 10 mg. dose is approximately equivalent to a 15 mg. dose of codeine. *Romilar* is available in double-scored 10 mg. tablets and in a syrup containing 10 mg. per teaspoonful.

Drugs Used in Cancer and Leukemia

Three anti-leukemic drugs have been released in 1954 to supplement such drugs as aminopterin already in use. Cancer research is progressing at a tremendous rate and more information concerning the disease is being made available daily. Indications seem to point to the fact that chemotherapeutic agents may prove to be the final answer in its treatment. However, in all probability no single chemical substance will serve in all therapy and a virtual battery of compounds may be necessary. The three products released are: Triethylene Melamine, *TEM* (Lederle); *Purinethol* (Burroughs Wellcome) and *Myleran* (Burroughs Wellcome).

Triethylene Melamine is 2,4,6-tris-ethylenimino-S-triazine. Its use is similar to that of the nitrogen mustards except that it is effective orally. It is employed in chronic lymphatic leukemia, chronic myelogenous leukemia, and Hodgkins' disease. It is given orally in an initial dose of 2.5 mg. daily. The drug is very toxic and must be used under very close medical supervision.

Purinethol is 6-mercaptopurine. It was developed as an adenine and hypoxanthine analogue on the theory that it might interfere as an antimetabolite with nucleic acid synthesis since both adenine and hypoxanthine are nucleic acid precursors. It appears that the drug may provide temporary remission, either partial or complete, of acute leukemia and of chronic myelogenous leukemia. It has not been found to be of value in chronic lymphatic leukemia, nor is it indicated in the treatment of solid tumors.

The use of *Purinethol* is not without decided danger. The dosage which will be tolerated or will be effective will vary from patient to patient and great care must be taken in adjusting dosage to avoid toxicity. The chief toxic manifestation is depression of the bone marrow resulting in leukopenia and eventually thrombocytopenia and bleeding. Since this drug may have a delayed action, it is important to withdraw the medication temporarily at the first sign of a fall in the white cell count. Since there is no antidote known at present

to counteract overdosage of *Purinethol*, it should be discontinued at the first sign of toxicity.

The product is available in 50 mg. scored tablets. The usual initial dose is approximately 2.5 mg./Kg.

Myleran is 1,4-dimethanesulfonoxybutane. It has been shown to be of value in the treatment of certain cases of chronic myeloid leukemia. It depresses both normal and abnormal myeloid tissue. The drug is claimed to be more selective than nitrogen mustard or the folic acid antagonists in its effect on myeloid cells and it may be somewhat safer in use. The drug has not been found to be of value in the treatment of acute myeloblastic, lymphoblastic or monocytic leukemia.

Myleran has been found especially useful for patients in whom radiotherapy has been abandoned. It also is quite toxic and careful hematological control is necessary lest irreversible depression of marrow function result. *Myleran* is available as 2 mg. tablets and is given at a dosage level of 4-6 mg. daily until clinical improvement or toxicity results. Complete blood counts at weekly or more frequent intervals are suggested and dosage must be individualized.

Central Nervous System Depressants

Probably one of the most important therapeutic advances made in the past year has been in the field of neuropsychiatry. The effectiveness of reserpine as a tranquilizing agent and the introduction of chlorpromazine have revolutionized the treatment of psychiatric disorders.

Introduced in this country as *Thorazine* by Smith, Kline and French, chlorpromazine was originally suggested as an anti-nausea drug for use in disease induced, drug induced and irradiation induced nausea as well as in nausea of pregnancy and in vomiting in children. However, after a short time, it became apparent that the drug had some much more important uses. Since it possessed a unique depressant action on the central nervous system, particularly the hypothalamus, it has been found to be of unusual value in the symptomatic control of certain neuropsychiatric disorders. In addition, it potentiates greatly the action of analgesics such as morphine making it possible to reduce the dose of the narcotic drug.

Thorazine has proved to be particularly effective in controlling severe agitation and acute anxiety such as occur in manic-depressive

psychoses, schizophrenia, senile psychoses, and in psychoneuroses. Agitated, anxious, protesting and rebellious patients become quieted and apathetic when given the drug. This assists not only in the control of the patient, but greatly facilitates psychotherapy.

Duration of treatment and dosage usually is dependent on the patient. Medication, however, should not be stopped abruptly. Even where improvement is shown dosage should be decreased gradually.

A drug having so many diverse pharmacodynamic properties is not without certain possible side-effects. It may cause drowsiness which, of course, may be desirable in certain cases. Transitory postural hypotension has been reported and in several cases this has precipitated a mild hypotensive crisis. Jaundice has been observed in a small number of patients receiving the drug, which of course, is a disturbing side effect. Although its pathogenesis and significance are not clear, the jaundice appears to be of the regurgitation type and has disappeared following withdrawal of the drug.

Other signs of the effect of the drug on the autonomic nervous system are the occurrence of dryness of the mouth, nasal congestion, some constipation and in a few patients, miosis. In addition, a small number of patients have mentioned the increased occurrence of emotionally intense and vivid dreams during *Thorazine* therapy.

Chlorpromazine is supplied in 10 mg., 25 mg., 50 mg. and 100 mg. tablets and in ampuls containing 25 mg. in 1 cc. and 50 mg. in 2 cc. sizes.

Meratran—(Merrell) is another drug which has been shown to be beneficial in certain neurogenic conditions. At its inception and during clinical trial it was described by the lay press as a cure for the "blues." It is available in 1 mg. tablets and recommended to relieve emotional and mental depression, psychogenic fatigue syndrome and to elevate depression of mood.

Dermatologicals

Ayerst Laboratories introduced two related products for the prevention of contact dermatitis. Known as *Kerodex,* they are protective creams formulated to provide a barrier between the skin and the irritant substance. They may be applied to the face, hands, or any other area of the skin.

There are two types available, the first *Kerodex 71* (water repellant) for wet work, is claimed to protect against shampoos, detergents,

bleaching and washing compounds, fruit and vegetable juices, drugs in aqueous solutions, acids and alkalis; and *Kerodex 51* (water miscible) for so-called dry work, protects against dust, grime, furniture polish and waxes, solvents, paints, cleaning fluids, oils and greases.

Schering Corporation have made sodium sulfacetamide available in lotion form for the treatment of seborrheic dermatitis. Known as *Sebizon,* it is available in a plastic squeeze bottle and contains 100 mg. per Gm. It is suggested for scaling dermatoses such as dandruff, acute and chronic seborrheic dermatitis; bacterial infections of the skin, and to relieve itching in common dandruff.

Diagnostic Aids

A large number of diagnostic aids have been made available over the past year. These are frequently as important as new drug discoveries since they permit diagnosis which heretofore have been either quite difficult or impossible.

Blastomycin (Parke Davis & Co.): A sterile filtrate from the culture of the mycelial phase of *Blastomycetes* grown on liquid synthetic medium, it is a definite aid in the diagnosis of North American blastomycosis and its differentiation from other infections. It is supplied in two 1 cc. vials, one containing .01 cc. of Blastomycin and the other containing 1 cc. of diluent.

Brucella Abortus Tube Antigen (Lederle Laboratories): A new tube agglutination test for the laboratory diagnosis of human brucellosis. The product is prepared from a designated stable strain of *Brucella abortus* recommended by the Committee on Brucellosis of the National Research Council. The product lends itself to a uniform procedure which can be utilized by all laboratories. It is available in 5 and 25 cc. vials.

Cholografin (E. R. Squibb & Sons)—Chemically it is the sodium salt of N,N-adipyl-bis (3-amino-2,4,6 triiodo)-benzoic acid and contains sodium citrate as a buffer and disodium ethylenediamine tetracetic acid as a sequestering agent. It is suggested for rapid intravenous cholangiography and cholecystography. It is intended primarily for the visualization of the biliary ducts. It may also be useful in those patients in whom adequate visualization of the gallbladder

cannot be obtained with orally administered contrast media. After administration of the drug, the biliary ducts may be visualized within about 25 minutes, while the gallbladder is filled for optimal visualization within 2 to 2½ hours. The product is available in two 20 cc. ampuls with two 1 cc. ampuls for sensitivity testing. It is essential that a sensitivity test be performed on each patient before use.

C. R. P. Antiserum (Schiefflin)—*C-reactive Protein Antiserum* is for the detection of inflammatory processes. The product is recommended to test for the presence of certain bacterial infections, to determine the correct dose of such anti-inflammatory drugs as cortisone, ACTH and the salicylates and in detecting latent rheumatic fever, and subacute bacterial endocarditis. It is available in 1 cc. vials.

Furadantin Diagnostic (Eaton Laboratories)—A diagnostic method to determine the effectiveness of this antibacterial drug. It is available in tablet form containing 10 mg. of nitrofurantoin. The tablet is plated with a sample of urine and a determination of bacterial sensitivity is made.

Histalog (Eli Lilly & Co.)—A histamine analog, this product is recommended to replace Histamine Acid Phosphate in the testing of gastric secretion, producing almost no disturbing side effects to the patient. It is claimed to reduce such associated effects as headache, flushing, and hypotension with faintness and syncope. Histalog's effect on the gastric secretion is quantitatively the same as that of histamine. The product is administered intramuscularly or subcutaneously and is available in 1 cc. ampuls containing 50 mg.

Inulin (Warner-Chilcott)—An improved pure form of inulin virtually free of fructose, the product is made from the common dahlia. It is pyrogen-free and used in kidney function tests. It is supplied in 50 cc. vials.

Ketodase (Warner-Chilcott)—A purified enzyme extracted from beef liver, it is offered as an aid in steroid hormone investigation. It is an enzyme which speeds up chemical processes involving steroid hormones and will virtually free certain hormones held in complex structure thus enabling easier study. It is also used in the determination of the following common urinary steroids; hydroxycorticosteroids, ketosteroids, pregnandiol, estrogens and corticoid conjugates in human blood. The product is available in individually packed 50

cc. bottles containing 250,000 units and 200 cc. bottles containing 1,000,000 units.

Enzymes

A highly purified crystalline trypsin of pancreatic origin has been developed by the National Drug Co. Known as *Parenzyme,* the drug is administered intramuscularly in a sesame oil suspension. The injection of the product produces a dramatic reduction of various acute inflammations such as thrombophlebitis, iritis, iridocyclitis, and traumatic wounds. It is also of value in varicose and diabetic ulcers and early reports indicate very good results in such conditions as bronchitis, acute asthma, and subdeltoid bursitis.

It is given in an initial dose of 2.5-5 mg. injected deeply into the gluteal muscle 1-4 times daily for 3-8 days. Some patients may require only a few doses. In others with chronic conditions continued therapy may be needed. Trypsin is believed to activate the conversion of profibrinolysin to fibrinolysin, thus producing an effect on the local inflammatory process.

Parenzyme is supplied in 5 cc. vials containing 5 mg. of crystalline trypsin per cc. of oleagenous suspension. It is important to use a dry needle and syringe when administering this drug.

Hormones

Lente Insulins

The "lente" insulins developed by Hallas-Møller and co-workers in Denmark represent a new kind of long-acting insulin produced without the use of a protein modifying agent. Released by Eli Lilly and Company, the product has about the same duration of action as NPH insulin and is interchangeable with it for most patients. It is available in both 40 and 80 units/cc. sizes.

The duration of action of "lente" insulins is in direct proportion to some function of their particle size and several types are available. The "lente" insulins are poorly soluble zinc insulins precipitated in an acetate buffer. By using different methods of precipitation, the Danish scientists could obtain such insulin in either a crystalline or non-crystalline form. The non-crystalline, or amorphous, type they called "Semilente" insulin. It is a quick acting preparation the effect of which lasts about 12 hours. The crystalline type was named "Ultralente" because its action is prolonged, lasting in excess of thirty-six hours when injected into a diabetic patient. After clinical investigation, it was shown that a mixture of 30% of Semilente Insulin

and 70% of Ultralente insulin represented an ideal combination and today it is marketed as *Lente Insulin* in the United States.

The absence of foreign protein such as globin or protamine is the chief point of superiority with the Lente Insulin compared with other long acting insulins.

Glucagon—Another step toward the understanding of diabetes was taken with the announcement that crystals of a new, pure biological substance prepared from pancreatic exracts have been isolated by biochemists at Eli Lilly and Co. The substance known as glucagon, causes a brief rise in the body's blood sugar levels. It has been long known that a hyperglycemic factor existed in pancreatic extracts, but this is the first time it has been successfully isolated.

Aldosterone (Ciba)—This product still under clinical investigation is the newly isolated hormone from the adrenal cortex, electrocortin. It is the 30th hormone isolated from the adrenal cortex and chemically it possesses an aldehyde group which makes it unlike the other compounds. Its action has been described as being ubiquitous in that it shows activity similar to both the glucocorticoids and the mineralocorticoids. The usefulness of the compound is still unknown and only small quantities are presently available for study.

Hydrocortisone and related compounds

The use of hydrocortisone has increased greatly, especially in products intended for topical use. For such use, it is superior to cortisone. In various skin and eye inflammations, it is most effective when applied as a suspension or as an ointment. While it suppresses the tissue inflammatory reaction, it possesses no antibacterial effect. For this reason, it is being administered combined with certain antibiotics. Typical of such combination released last year are *Hydroderm* (Sharp and Dohme) and *Neo-Cortef* (Upjohn) which combines neomycin. (Hydroderm, also contains bacitracin); *Terracortril* (Pfizer) which utilizes Terramycin; and Chloromycetin-Hydrocortisone Ophthalmic which employs Chloromycetin. These combinations often produce dramatic results in infections accompanied by acute inflammation.

Hydrocortisone is also being combined with sympathomimetic amines for use in the nose in allergic rhinitis and similar conditions. Such a product is seen in the Smith, Kline and French product *Vasocort Solution*, which contains hydrocortisone (0.02 percent),

Paredrine Hydrobromide (0.5 percent) and phenylephrine hydrochloride (0.125 percent).

Hydrocortisone may also now be given intravenously using *Infusion Concentrate Hydrocortone* (Sharp and Dohme) and *Sterile Solution Cortef* (Upjohn). These are clear solutions containing 100 mg. of hydrocortisone in 20 cc. They are used where a rapid effect is needed such as in transfusion reactions, acute allergic emergencies, surgical shock, etc.

A new derivative of hydrocortisone was released during the latter months of 1954; namely, 9-alpha-fluorohydrocortisone acetate. The new drug is claimed to be ten times as potent topically as hydrocortisone. It inhibits inflammatory reactions to bacterial, allergenic, and chemical agents, and also has antipruritic action. The product is available from E. R. Squibb and Sons as *Florinef* in a 0.1 and 0.2 percent lotion and ointment and from Sharp and Dohme as *Alflorone Acetate* in a 0.1 and 0.25 per cent ointment.

Schering has anounced two new steroids representing a series of compounds of unusual potency which are believed to be several-fold more active in treating rheumatoid arthritis and other inflammatory diseases than the adrenocortical hormones; cortisone and hydrocortisone. The products are now under clinical investigation and are known as *Metacortin* (metacortandracin) and *Metacortalone* (metacortandralone).

Other Advances in Hormones

Several outstanding chemical advances were made in the field of hormone chemistry. The first of these was the fractionation of ACTH into several pure components each having physiologic activity. The molecular weight of each component appears to be too high to offer the hope of early synthesis, although it is possible that some fragment of one of the active polypeptides may possess physiologic activity.

Du Vigneaud and his associates also succeeded in synthesizing oxytocin and the complete structure of both vasopressin and oxytocin from posterior pituitary has been elucidated. Vasopressin is quite similar to oxytocin in structure except that in vasopressin, leucine and isoleucine fragments are replaced by phenylalanine and arginine.

Motion Sickness

A great deal of interest has developed in this group of drugs and one of the interesting developments was the release of several of these

compounds for over-the-counter sale. In addition, two new compounds were released. Both are somewhat related in structure; one is cyclizine (*Marezine*—Burroughs-Wellcome) which is N-methyl-N-benzhydryl piperazine monohydrochloride. It is identical with the antihistamine chlorcyclizine except that it lacks chlorine on one of the benzhydryl rings. It is available as 50 mg. tablets.

The other drug released was *Bonamine* (Pfizer) which has a N-*m*-methylbenzyl group in place of the N-methyl group as in *Marezine*. It is available in 25 mg. tablets.

Muscle Relaxants

A modified form of the well established drug mephenesin was made available by E. R. Squibb and Sons as *Tolseram* (mephenesin carbamate). Like mephenesin, the product has a selective blocking action on the internuncial system. However, blood levels are more prolonged and uniformly more persistent. It is used for the same conditions as mephenesin including the muscle spasm of rheumatic disorders and allied conditions. The drug is available in 0.5 Gm. tablets and in a suspension containing 1 Gm. per teaspoonful.

Nasal Decongestants

A new potent nasal decongestant was made available by Pfizer. Known as *Tyzine*, a brand of tetrahydrozoline hydrochloride, the product is chemically related to naphazoline. It differs in that it has one saturated ring and one less methyl group. It's primary advantage lies in the fact that it has relatively no effect on blood pressure or the central nervous system. However, it should be used with caution in small children since it seems to possess a somewhat hypnotic effect in such patients. It is available in a 0.1% aqueous solution for nasal administration.

Vasodilators

A new approach for the use of a vasodilator is characterized in the release of the product *Arfonad* by Hoffmann La Roche. The product is a short-acting vasodepressor agent for the induction of controlled hypotension during major surgery. It produces vasodilation through ganglionic blockade and direct dilation of arterioles. The drug is claimed to bring about a controlled and readily reversible hypotensive response..

The product is administered by intravenous infusion and is particularly helpful in neurosurgery, vascular surgery, fenestration operations and other procedures in which bleeding tends to obscure the operative field. *Arfonad* is available as the camphorsulfonate (trimethaphan camphorsulfonate) in 10 cc. ampuls containing 50 mg. of the drug.

Vitamins

C. V. P. (U. S. Vitamin). This product is Citrus Bio-Flavonoid which is said to be more active than rutin or hesperedin. The product contains natural vitamin P complex and ascorbic acid. It is indicated to improve capillary resistance by helping to overcome abnormal capillary permeability and fragility, thus acting to prevent bleeding and vascular accidents in hypertension and diabetes. It also helps to prevent capillary damage in X-ray therapy. It is available in 200 mg. capsules.

Gestatabs (White Laboratories) and Cyesicaps (Lederle)

These are two of what will probably be a series of compounds. They are prenatal formulas which are phosphorous free. Studies indicate that the absence of phosphorous may improve the typical leg cramps of pregnancy. In addition, some workers claim that calcium may be better absorbed as the lactate rather than as the phosphate.

Miscellaneous

Mestinon—A new drug developed by Hoffmann La Roche, this product chemically is the dimethyl carbamate of 3-hydroxy-1-methyl pyridinium bromide. It is reported to make life more comfortable for sufferers from myasthenia gravis. It is closely related to neostigmine, but initial studies indicate that it produces far fewer undesirable reactions than does neostigmine. The drug is still under clinical trial but early studies show promise.

Stilbosol—This is the name assigned to the veterinary product of Diethylstilbestrol Premix being distributed by Eli Lilly and Co. Research trials indicate that the product greatly stimulates the growth of fattening cattle. After extensive study, the Food and Drug Administration have released the product for this use. A great deal of the research was conducted at Iowa State College where studies indicated that the drug when properly used; cut feeds costs, increased daily gains by ½ to ¾ pound, and boosted the profit margin per steer.

THE PHARMACIST SERVES WITH MANY HANDS *

By George D. Beal **

ONCE in a while some one compliments me by asking about a professional career for a son or daughter. I am quite likely to suggest Pharmacy, but there often comes a quick negative, with comments on miscellaneous retail trade and long hours, concluding with a not-funny crack about a sandwich. Probably that person passes daily, and patronizes, a certain type of drug store, and assumes that this place is truly representative of the profession, the same sort of reasoning used by the four blind men who attempted to describe an elephant. Because that person may have never been behind the screen of the prescription department or seen pharmaceutical industry at close hand, he can have no idea of the many professional roles in pharmacy.

The professional responsibilities of pharmacy include every service from finding the crude materials from which modern drugs are prepared to the compounding of the physician's prescription. The steps that go to complete that prescription include:

1. The collection and refining of the basic materials used by the pharmaceutical chemists.

2. Chemotherapeutic and clinical research to evaluate new drugs and especially to develop new and more efficient types of medication.

3. The control, by supervision and analytical technique, of manufacturing operations.

4. The development of more effective dosage forms.

5. Pharmaceutical manufacturing.

6. The proper preservation of pharmaceuticals.

7. Advertising, detailing, and wholesale distribution.

8. Quality control during distribution, including the enforcement of the "pure drug" laws.

9. Retail distribution, including the compounding of the physician's prescription.

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** Director of Research, Mellon Institute, Pittsburgh, Pa.

Let us see how from the unaided and untutored hand of the prehistoric medicine man this pharmaceutical team has come together. Most of the romance of pharmacy has been behind the scenes. We can only speculate as to the origin of pharmacy and the "materia medica", the tools and materials of pharmaceutical science. It has been said that "when man emerges into history, he has a dog by his side and an apple in his hand", to which we can add that he also has about his person some herbs to relieve a stomach ache. The beautiful series of lunettes in the Library of Congress tracing the evolution of the book from oral tradition to the printing press of Gutenberg, is a pictorial explanation of why we can do little more than wonder how things began, for so much of the historical element has been distorted or lost. No one can say how much of the practice of medicine and pharmacy came from ancient China or from India, from Assyria, Egypt, or Greece.

Some writers on comparative religion maintain that religious belief arose because we were afraid of the unknown. If our early pains were of mysterious origin, which we were unable to understand, we turned to the men who studied and spoke for such mysteries. Since the priest was the one person who, by the manner of his calling, had time for learning, he could more easily be the person who had learned to give relief from physical pain. The universities sprouted and began to grow under the shelter of religious colonies, the only places where speculative scholars might be found. Speculation on the mysteries of religion led naturally to speculation on the mysteries of the universe, from which science had its birth.

Life is precious, and gold helps one to enjoy life. To a student of the mysteries the preservation and prolongation of life was a challenge; and since there were potions that apparently had the power of rejuvenation, why might not one be known, in fact as well as in legend, that could be an elixir of life, just as there might be a philosopher's stone to transmute base metal into gold. Metals were actually won from earth by fire, so why might not the precious metals be won thus from the brasses and bronzes? With many of the characteristics of chemical reactions being known as attributes of Satan, alchemy may well have been called the black art for other reasons than its being practiced in Khem, the land of the black soil, otherwise Egypt. A scholar might apply his art with less suspicion of being in traffic with the Devil if he made an effort to utilize his magic in the cure of disease. We speak with a great deal of pride of those apothecaries, like Scheele,

who were great architects in the foundation of chemistry, without thinking that possibly some of them only put on the robe of the apothecary in order that they might practice their beloved chemistry.

The basic sciences dealing with matter are chemistry and physics; and with life, biology; and these three in turn find among their most effective applications pharmacy and medicine, with pharmacy receiving too little of the joint credit for its contribution to the conquest of disease, because so much of the work of pharmacy is behind the scenes. It is quite generally agreed that one of the gambits of modern chemistry was William Perkin's synthesis of mauve which laid the foundation for the synthetic dyestuffs industry. But Perkin was not looking for a dyestuff. Aniline had been recognized as a product of the destruction of quinine, and Perkin was trying to go backwards from aniline to quinine as part of the effort to make Britain's many colonies safe for the white man in the presence of malaria.

It makes comparatively little difference whether we are speaking of metallurgy, or textiles, or pharmaceuticals. Man's first efforts have always consisted of turning to his own use that which he could find at hand in nature. His first working of metals made use of nuggets of copper or gold, or of meteoric iron. He used the natural bark cloth from some trees, or the skins of slain animals, for protection against the weather, and mineral waters, salts, or herbs, when he felt unwell. He learned other things from these uses.

He learned that a sling extended the length of his arm so that he could throw a stone farther and with more force. He could point a stick in a fire, and stab an animal or any enemy to death with greater ease than by beating him over the head with the same stick. If the stick was long and well balanced, it could be hurled many times the length of his reach. So also came bows and catapults. These things became tools of war as well as of chase, but they brought man down out of the trees and helped him to walk upright. The more intelligent of the coming humans who lived on grains and nuts found that cracking improved edibility, and then that certain selected stones were easier to use for cracking, pounding, rubbing, or rolling; until one day one of them invented the mill.

Wiser men learned by observation which herbs and earths were of the most promise in medicine, and concocted theories, such as the doctrine of signatures, to help them explain the behavior of drugs, hoping thereby to be able to search out new and more useful drugs. Then came chemistry with the early chemists delving into the com-

position of matter. That which was learned from the earths was applied to the ashes, then to the plants themselves, and active principles of drugs were discovered. Then came the time when the simpler plant educts were prepared in the laboratory from apparently unrelated sources, and the beginning of the modern synthetic era of chemotherapy was reached.

Go back for a moment, if you please, to our native textile fibers—linen, cotton, and wool. I suppose it is possible to believe that the Creator gave man intelligence to use these several things for his own good, which intelligence he might later train to the point where he could give nature some assistance. Nature has certain patterns of her own which she insists on following. She may yield to us on some details, but in some other ways she is inexorable. Her fibers are of cellulose, or keratin, or serine, but they hold to different patterns forced by the differences in the cells that produce them. Synthetic fibers are extending the use of natural fibers, making it possible to draw upon the latter's good qualities to the limit while supplanting their deficiencies with superior man-made qualities. The blending of natural and man-made fibers to produce new and superior fabrics is quite analogous to what pharmaceutical chemists have been doing for some years in their field, only a bit more tangible because anyone can feel for himself the "hand" of the fabric.

We first took nature's drugs, like her fabrics, very much as we found them. Then by exploration, selection, and breeding we discovered or developed higher potencies. We learned what we could about their standardization, their most effective preparations, their preservation, the indications for their use and the idiosyncrasies that accompany their use. Most important of all, we have with great success determined the composition of their active principles to the extent of identifying the individual building blocks in the molecule and the place each block occupies in the molecule. We have learned, while building comparable molecules from these same blocks, just what effect each block has when introduced into the animal body, to what extent depends upon the placement of the block, and how the relative position of the block with regard to other blocks affects the behavior of those other blocks. Thus has been laid the foundation for the wedding of chemical and medical science into the family of chemotherapy, the pioneering part of modern scientific pharmacy.

This new field which provides part of the magic for prescription practice is by no means so much a division of chemistry or medicine

as it is of pharmacy; it has broadly increased the scope of pharmacy and brought many newly trained workers in from other fields. Many of the rules by which chemotherapists work have been developed by the study of natural products. The basic impetus to the development of antimalarials was derived from the study of quinine, itself the first purified antimalarial. But quinine was not in the first place tested as an antimalarial in an effort to find some use for it. A missionary in Peru is alleged to have learned that natives used the bark when suffering from relapsing fevers, and to have made it available to the Countess of Cinchon in her similar illness. Hence came the names "Jesuit's bark", and "cinchona", and the German "China", so that Pelissier and Caventou, the apothecary discoverers of the new bases which seemed to retain the properties of the bark, properly named these cinchonine and quinine. The crystalline derivatives that Serturner then isolated from opium were for somewhat similar reasons named narcotine and morphine, the first signifying torpor; the second, sleep. Perhaps today it would be considered bad taste to coin these latter two names because of their therapeutic suggestiveness.

There are some pretenders to scientific attainment as well as some misguided scientists who even now assert the superiority of natural over synthetic substances, even though the most critical tests fail to show a distinction. When Wohler in 1828 produced urea, previously known only from natural sources, by heating the unquestionably inorganic ammonium isocyanate, he broke a hole in the wall that had separated the earth from the life upon it. In 1860 Kolbe produced salicylic acid, hitherto known as of vegetable origin, from phenol which was only known as a by-product from coking of coal. When a new building is erected on Park Avenue today, construction workers generally wait until the wreckers have demolished the old building and hauled away the bricks and mortar before beginning the new structure. I interrupt myself to remember that Charles F. Chandler, in his lectures across the quadrangle in 309 Havemeyer, said as of 1910 that buildings were torn down and the bricks reused so many times in New York City that they automatically piled themselves whenever a building was pushed over. What I was going to say is that with the present advancement of chemical science, if a natural compound of promise is discovered, the structural organic chemists are trying to break it down for structural determination before it is fully evaluated as a drug, with the synthetic chemists hard on their heels picking up stone after stone as they fall from the

analyst's hands and trying to fit them together again. The haste is that of the engineer who cannot wait for blueprints but must work from the pencil sketches.

Then we have those scientists, so zealous in the support of their calling that they maintain in every public utterance that whatever nature can do man can do better. Whether the subject is textiles or pharmaceuticals, the synthesists, and this means many of our teachers, write off in every public utterance nearly everything coming from the natural world, leaving the remainders to undergo a certain amount of manhandling in the laboratory. They do well to take nature as a model, but they should grant to nature certain excellencies and certain valuable structures that so far they have been unable to achieve by their hands. I dare say we can feed the world on plankton and algae and leave the land area for more useful purposes, but just once in a while it is nice to have biosynthesis and photosynthesis produce a thick steak and hashed brown potatoes.

The decision as to whether those who study natural products or those who have dealt with purely synthetic materials have contributed the most to conquering disease with drugs is only swinging on the tip of a pendulum. Like textile fibers, whether natural or man-made, the medicinal chemicals from either source have their good and their bad features. The search for a synthetic replacement for morphine, for example, is not to improve on morphine as an analgesic, but to secure in a synthetic replacement that does have these analgesic properties a freedom from the withdrawal symptoms that constitute habituation.

When vegetable drugs failed to bring security in the treatment of the pneumonias it was said that the most important factor was good nursing. Then microbiologists and biochemists took a step forward through typing of the pneumonias and the development of specific serums. Next chemists developed the sulfonamides, which the medical profession used with much success as systemic anti-infectives, but with such eagerness that unfavorable side reactions almost neutralized the benefits of the principal effect until physical chemists, having in mind the laws of solutions, came forth with the polypharmacal suggestion of using two or three sulfas combined as fractional doses while the arithmetical sum constituted a therapeutic dose.

Then an inquisitive microbiologist, who had observed and thought about the effect of mold exudates on his bacteriological plates, opened up the enormous field of antibiotics, and we found ourselves once more

depending upon the purified metabolic products of plant life, but this time the plants were microscopic rather than macroscopic. The discovery of penicillin was only the first of many antibiotics to be obtained through frantic examination of all known varieties of molds. It also opened the door to welcome two new divisions of chemistry into the pharmaceutical circle. These compounds being produced by a species of fermentation processes, and in such low concentrations as to require their extraction from enormous volumes of liquid gave chemical engineers a field day in the design of new pharmaceutical equipment. And, for the first time, the pharmaceutical industry was called upon to dispose of huge volumes of liquid wastes having the oxygen demand and putrefactive capacity of human wastes, so that sanitary engineers were called into pharmacy to take care of its trade wastes.

Probably no other group of medicinal agents has had the concentrated study put upon it that the antibiotics have enjoyed. Neither has any other group benefited as have the antibiotics from the enormous sums spent in process development. No other group of drugs has come to light at so critical a time in history, when almost the entire world was plunged in the greatest of wars. Wars have had a great deal to do with the development of medical science. Nursing and hospitalization achieved dignity during the Crimean War, sanitation and the control of infectious disease in the Spanish-American War; plastic surgery and aseptic treatment of wounds in World War I; and the anti-infectives and antibiotics in World War II. Given a certain degree of scientific knowledge and technique, the speed with which a new discovery is achieved, evaluated and made commercially available is to a large degree proportional to the concentration of the attacking force in terms of available scientific personnel and financial support. Therefore, we can anticipate a greater number of developments of this sort in a period of national stress.

No, we cannot write off either the natural or the synthetic medicinal agents with which pharmacy deals. Such natural products as the digitalis glycosides continue to hold their place in medicine. Epinephrine and ephedrine are today synthetic rather than natural only because chemists have learned how to put together their simple structure. Cocaine was isolated from coca leaves in 1855, and its numbing effects upon mucous membranes made of note thereafter. It was not used deliberately as a local anesthetic in surgery until 1884, opening a new field in surgical technique. The proof of its

structure was arrived at between 1885 and 1895, when the study of analogues began, and procaine, or novacain, to give it the name under which it was first introduced, was synthesized in 1905. Local anesthesia has been under constant study since that time, but in the last fifty years it is hard to say that a more acceptable all-purpose local anesthetic has been prepared. Finally, when curriculum planners in our colleges are wondering what to do with pharmacognosy because of the decadence of vegetable drugs, we find ourselves all agog about the Rauwolfias for the control of hypertensive conditions.

Scientific activities run in waves, with interest directed first this way and then that. For quite a number of years a few people held together a little Division in the American Chemical Society called the Division of Pharmaceutical Chemistry. It was barely tolerated, largely because the analytical chemists in their division did not care to recognize these few control chemists. Then suddenly the chemistry of drugs was recognized by the organic chemists and the group became respectable, but as a Division of Medicinal Chemistry. Its interests now are so vast that since this interval of about 35 years no national program can encompass all that the members wish to talk about.

I interview a good many candidates for research positions in chemistry, and, agreeing with statistics, find that a very substantial majority of them have taken their doctorate in organic chemistry. In an organization such as Mellon Institute, our major needs are for persons versed in organic and physical chemistry and in chemical engineering. Our needs for organic and physical chemists are pretty well intermingled, but as basic sciences rather than as forms of laboratory application. Consequently, after I speak at some length and enthusiastically of the opportunities in some sector of the textile industry, for example, the young man very kindly and patiently tells me that I have evidently misunderstood him, because he is an organic chemist. Of course, he means that his thesis involved the synthesis of one or more important new compounds for the Formula Index of Chemical Abstracts, because a good synthetic problem is the backbone of a quick thesis. But there is in the young person's mind something more than the mere desire to continue the arrangement of molecules. In my day as a graduate student every new compound was, if possible, diazotized and coupled in the search for a dyestuff that would outshine the rainbow's brilliance. Now most young organic chemists picture themselves as the discoverer of

the wonder drug that will be the long-sought elixir of life. The rest are laboring over the gunks and goos that we could not clean out of our beakers, trying to find in them a textile fiber of universal appeal, or a molding plastic to take the place of all old structural materials.

Steel is one of America's great industries, and many speak of it as being at one time the only industry subjected to scientific control, and of how other ironmasters thought Andrew Carnegie had lost his senses when he insisted that a man in a laboratory might see farther into a tap of iron than the foreman on the furnace platform who "knew" what went into his furnace. Yet pharmaceutical manufacturers before that were turning out laboratory-standardized remedies and saving lives thereby. There is considerable speculation among chemists as to whether a manufacturer of explosives or of electrical machinery was the first to create a research laboratory; but actually the first important laboratory building dedicated to industrial research was erected by one of our great pharmaceutical manufacturers, and students of research laboratory organization frequently turn to the pharmaceutical industry when they wish to examine practical experience in research management.

The many tools available to the prescriptionist today are causing a new face to come over pharmacy. Although a ferment was stirring earlier, the beginning of the Pharmaceutical Survey in 1946 brought into the open dissatisfaction with the program of pharmaceutical education. While this century has already seen more evolution in pharmaceutical education than in the preparation for practice of any other profession, the program was directed almost in its entirety to the training of retail pharmacists in a certain mold. At the beginning of this century it was possible for a boy to enter upon a total of only one year of actual instruction in a first-class college of pharmacy without having set foot in high school. The first twenty years brought about a requirement of high school graduation and three years of professional education. The year 1932 saw the consummation of the collegiate course in pharmacy leading to the bachelor's degree by way of a mandatory four-year curriculum.

When these changes began, our colleges tended toward the private proprietary variety rather than being affiliates of institutions of higher education, especially those enjoying state support. Their dependence was largely on student fees, and their students were dependent in turn upon employment by the pharmacists of the area. The schools were

frequently organized and maintained by area pharmacists in order to provide bare compliance with the laws regarding education and registration. There were three stock arguments against each proposed advance in the educational program, always to the effect that

(a) Students cannot afford and will not pay for so much education.

(b) The needs of pharmacy will not justify so much education.

(c) It is hard enough to get drug clerks now, and by driving them out of the schools the supply will be further decreased and salaries magnified beyond present figures.

There has been such a sameness about these objections, regardless of the advancement proposed, that I imagine they were first uttered against the proposed change from apprenticeship to formalized training when the New York, Massachusetts, and Philadelphia Colleges of Pharmacy announced their first offering of regular instruction. The colleges have gone boldly forward in the face of opposition, with the result that we have today seventy-five colleges accredited by the American Council on Pharmaceutical Education, approximately 92 per cent of them satisfying the requirements for a Class A college, with the remaining ones engaged in campaigns for affiliation, building, or adequate sustaining funds to remedy their deficiencies.

We have been training pharmacists from the beginning in the fundamentals of pharmacy and, regardless of the length of the curriculum, pressing into it all the scientific background of pharmaceutical practice that students could absorb. Even though retail pharmacy today is not manufacturing chemicals and compounding polypharmacal prescriptions as of a century ago, dispensing the modern drugs of high potency and infinite variety requires a more intensive training in the basic sciences of pharmacy. Then the complex ways of business require managerial training that filled the curriculum to bursting. Finally, in order to fill the positions of responsibility and to command the respect associated with professional men, education must include the more fundamental of the humanities. In order to give adequate professional training in pharmacy, an increasing number of colleges have been experimenting with the plan of comprehending all the professional study of pharmacy in three years, but requiring as a prerequisite for entrance to professional study two years of collegiate

training in the humanities and the basic sciences, with such success that currently about 20 per cent of all the accredited colleges are on a 1-4 or 2-3 basis, which will become the standard pattern of pharmaceutical education in 1960.

At the beginning of my talk I spoke of all the areas into which pharmacy divides itself. My reason for doing so was to lay the foundation for saying that these areas may be staffed by pharmaceutically trained personnel, that desirably they are and will be so staffed, and that failure to satisfy along these lines will be the fault of the colleges and those whose voices are listened to in the colleges, the alumni.

It is a perfectly natural wish that the supply of professionally trained personnel shall not exceed the demand. Those, however, who think of pharmacy graduates only as retail pharmacists, and who would have college registration and graduation held down to the annual replacements in the retail trade are not looking forward to the broader needs of pharmacy. This line of reasoning must be successfully overcome if pharmacy in all its branches is to be adequately supplied with pharmaceutically trained personnel.

In surveying the educational program of pharmacy, we must think of it as training persons to serve on at least two levels, which is not uncommon in professional education. At the one level we find the everyday practitioners of medicine, dentistry, law and pharmacy. These are the professional men who are expected routinely to meet the public daily, and service the profession daily. Teaching and research go beyond daily problems, and can be well served only by a program of graduate study beyond the bachelor's level. We have always had in this country a few schools that excelled in the production of scholars. These excelled, however, because back in their youth one or more members of their family developed a spirit of inquiry and a taste for research that led to the establishment of a real tradition in that institution.

If the younger scholars moved to another school that provided receptive and fertile soil a new center of higher education in pharmacy germinated. If, on the other hand, the spirit of that school stood with one hand on the cash register, if there were no pupils to sit at the teachers' feet, if there was no sympathy in the remaining faculty or the governing board, and no kindred spirits in the state association, either the fire of learning was extinguished in that person, or more likely, he moved from education to industry, for education's loss.

The provision of ample opportunity for graduate study in the colleges of pharmacy is necessary not only to provide new blood for the faculties and for the research laboratories of the industry, but also for its beneficial effect upon faculty morale in the school maintaining graduate programs.

One college president, critical of all accrediting agencies, sought to change the subject during an accreditation visit by asking, with considerable emphasis, why pharmaceutical industry did not provide graduate scholarships for training persons for education and research. It was a pleasure to tell him something that his dean had apparently forgotten to do, that on his faculty were two young men who had obtained their doctorates with the aid of fellowship grants from the American Foundation for Pharmaceutical Education, and that with the provision of any research facilities whatever his faculty could shortly be in a position to direct research under similar grants.

The pharmaceutical profession should acknowledge a substantial indebtedness to those men who conceived the idea of this Foundation for planned support of education, and who through their sincerity and known integrity persuaded the manufacturers whose income was derived from pharmacy to contribute to the funds of this Foundation. And we are equally indebted to the donors of these funds for recognizing the needs of pharmaceutical education. The Foundation has made possible the Pharmaceutical Survey, the extensive work of the American Council on Pharmaceutical Education in the development of accreditation standards and the accreditation program itself, and several hundred scholarship and fellowship grants.

There are on the horizon changes in the face of pharmacy. The present collegiate course in pharmacy was developed in the greatest of depressions, and its earliest graduates soon faced the conditions created by the greatest of world wars. Those graduates are only beginning to attain middle age today, and they probably do not represent more than a bare majority of the practicing pharmacists. As their majority grows, as we find them gradually becoming the sole voice of pharmacy, we can anticipate a general face-lifting in the practice of retail pharmacy. For me that time will come when, riding down town on a street car, I can always tell with certainty several blocks away whether I am approaching a retail pharmacy or a numbers joint.

It is only fair to say that the changes taking place in pharmaceutical practice constitute evolution rather than revolution. There is throughout a pattern of scholarship, which has been guided by reason

and later by science as science has been able to understand and explain the laws and the phenomena of nature and the processes of life. It is not assumed that pharmacy, as one of the health sciences, will ever produce the elixir of life sought by the alchemists. But the labors of the sciences represented in pharmacy, whose products form the prescription stock-in-trade of the corner pharmacist, taken with the ever-growing knowledge of the medical practitioner, have demonstrably lengthened the human life span so that statistically the end of life comes not from infectious diseases but from degenerative diseases. It is fitting that a machine, even a good machine, should wear out, to be replaced by a new and improved model, and we may properly look at the termination of human life in the same way. The many hands with which the pharmacist serves bring safety to childhood, well-being to middle age, and comfort to old age. The pharmacy that every one sees is but one of the outriders of a mighty army whose sole concern is the protection of public health through provision of tools for the prevention and amelioration of disease. It is a distinguished profession capable of maintaining its own self-respect, and its agencies, particularly its colleges, are to be congratulated upon the fearlessness with which they have stood for a better profession.

A PHARMACOGNOSTICAL STUDY OF THE ROOT OF *RAUWOLFIA BEDDOMEI* HOOK. F.*

By Heber W. Youngken

THE root of *Rauwolfia Beddomei* Hooker filius, a shrub native to India, has been occasionally found as a substitute for *Rauwolfia serpentina* root in commercial lots shipped to this country. Its physical characteristics and histology are described. Qualitative chemical tests show the presence of alkaloidal material in this substitute.

This root resembles that of *Rauwolfia serpentina* in its structural features more than that of other past substitute and adulterant roots of *Rauwolfia* species heretofore recorded and described. Casual examination of cross-sections in ascertaining its presence in commercial lots purported to represent *Rauwolfia serpentina,* therefore, may be deceptive. Like *Rauwolfia serpentina* root, it possesses stratified cork appearing as alternating zones of larger and radially broader and smaller and radially narrower cork cells; its individual starch grains are numerous and of similar general forms; its wood wedges are of similar general appearance in respect to the arrangement of the vessels and fibers, and there is an absence of sclerenchyma in the secondary phloem of some of the cross-sections. It differs from *Rauwolfia serpentina* root in exhibiting stone cells in the secondary phloem, although these are not seen in every cross-section, in its curved xylem rays, in possessing more numerous xylem ray cells of larger size (up to 152μ in width), and in its compound starch grains, more of which possess one of the components smaller than the others.

* Abstract of Paper presented to the Pharmacy Section, A.A.A.S., Berkeley, California, December 28, 1954.

SELECTED ABSTRACTS

Cosmetic Applications to the Skin and Their Effect on the Acid Mantle. Jacobi, O., and Heinrich, H. *Drug and Cosm. Ind. 75:*34 (1954). The acid mantle of the skin is the first line of defense of the body against chemical and microbiological attack. It is composed of a variety of components carried by the sebum. The acid nature of this mantle is largely due to acids such as various amino and lower fatty acids, lactic, oleic, uric, and acid salts such as bicarbonates. The buffer capacity of this mantle is associated with the amphoteric nature of the free amino acids, protein degredation products, bicarbonates, and possibly ammonium salts.

The acid mantle is often removed during washing, by abrasion, or by the mere every day activities of the person. The speed with which this mantle is rebuilt varies with the cause of its removal but, following a mild soap wash and adequate rinse, the sebum with about 50 per cent free oleic acid will reform about 80 per cent of the original layer within 60 minutes.

The pH of various portions of the facial skin was determined electrometrically on 22 persons. It varied from a low of 4.2 to a high of 8.1, the latter on a person with acne. The majority of the determinations ranged between about 5.0 and 6.5.

The authors found that soap is a good cleanser for most skins provided the soap is removed by thorough rinsing. Rinsing restores the acid mantle very rapidly. The buffer capacity of the skin was also determined by the application of alkaline solutions and creams. The buffer capacity varies from person to person. When the normal buffer capacity was used up it was found that the only remaining neutralizing effect was obtained from the amphoteric nature of the keratin of the epidermis. The authors concluded that cosmetic preparations should be formulated so as to aid the barrier action of the acid mantle. They also pointed out that cosmetic formulations should not have a high buffer capacity in themselves so as not to overcome the buffer capacity of the normal acid mantle.

Oral Penicillin in the Treatment of Upper Respiratory Infections. Cronk, G. A., Naumann, D. E., McDermott, K., Menter, P., and Swift, M. B. *Am. J. Med. 16:*804 (1954). The use of antibiotics in the treatment of many self-limited and relatively harmless diseases has continued to increase in recent years in spite of the fact that there are no proven therapeutic benefits but there are increasing reports of serious toxic reactions. The authors reported the results of a study in which the following compounds were used and the results compared in a series of 2177 cases of upper respiratory infections:

	R1	R2	R3
Acetylsalicylic acid	0.160 Gm.	0.160 Gm.	0.160 Gm.
Phenacetin	0.128 Gm.	0.128 Gm.	0.128 Gm.
Caffeine	0.032 Gm.	0.032 Gm.	0.032 Gm.
Phenyltoloxamine dihydrogen citrate	——	0.025 Gm.	0.025 Gm.
Procaine penicillin G	——	——	100,000 units

In a controlled study of 62 hospitalized patients in which formula R1 and R3 were used, the subjective response, objective findings and febrile course of the disease were essentially the same in the two groups. Of 659 ambulatory patients who were treated with compound R1, 2.8 per cent ultimately required infirmary bed care. Of 764 ambulatory patients who received compound R2, 3.6 per cent required bed care and of 754 ambulatory patients receiving compound R3, 4.7 per cent required bed care. Although not statistically significant, there is the suggestion that there was a prolongation of illness among the patients receiving penicillin.

Salicylamide was substituted in a dose of 0.32 Gm. for the aspirin compound portion of the above formulas in an additional 340 patients. No significant difference was observed in these cases.

Toxic reactions to penicillin were extremely uncommon among the patients treated in this study. Only one patient developed serum sickness. Gastric irritation developed in 0.79 per cent of the patients receiving compound R3, but such irritation also developed among 0.26 per cent and 0.15 per cent receiving compounds R2 and R1, respectively.

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